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09/508,745	07/12/2000	SUZANNE CORY	13464	7536

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EXAMINER

BERTOGLIO, VALARIE E

ART UNIT PAPER NUMBER

1632

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/508,745

Applicant(s)

CORY ET AL

Examiner

Valarie Bertoglio

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 18 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3,9,12,14,16-18 and 20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,9,12,14,16-18 and 20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03/125/2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/18/2005 has been entered.

Claims 2,4-8,10,11,13,15 and 19 have been cancelled. Claims 1,3,9,12,14,16,18 and 20 have been amended. Claims 1,3,9,12,14,16-18 and 20 are pending and under consideration in the instant office action.

### *Claim Objections*

Claims 1,3,9,12,14,16-18 and 20 remain objected to as being drawn to non-elected subject matter. Claims 1,3,9,12,14,16-18 and 20 continue to encompass disruption of non-endogenous bcl-w genes (Non-elected groups II,IV and V), including non-bcl-w genes (claims 1,3 and 20). Claims 14 and 16 are drawn to introduction of an antisense molecule, which is subject matter of non-elected Invention II. Claims are not limited to the elected invention which is a genetically modified non-human animal having reduced levels of Bcl-w protein as an effect of a genetically modified, endogenous bcl-w gene.

Applicant argues that the claims are now drawn to the elected subject matter. This argument is not persuasive. The claims merely require a reduction of bcl-w protein and that the animal be genetically modified. No relationship between the genetic modification, the endogenous bcl-w gene and levels of Bcl-w protein is required by the claims. For example, claim

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1 should require that the endogenous bcl-w gene be genetically modified and claim 14 should read "the endogenous bcl-w gene" at line 4.

Claim 14 is objected to because of the following informalities: Claim 14 has been limited to a mouse species, however, at line 5 it continues to refer to an animal. The scope of "animal" is not consistent with the breadth of the claimed "mouse" (line 2).

Appropriate correction is required.

***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description***

Claims 1,3,9,12,14,16-18 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' arguments on pages 5-6 of the response filed 04/18/2005 have been fully considered and are partially persuasive. Applicants have amended the claims such that they no longer encompass non-mouse species and no longer encompass animals with reduced levels of any protein having 47% similarity to bcl-w. However, the claims continue to encompass a genetically modified mouse comprising reduced levels of a functional derivative of bcl-w wherein the genetic modification can be in any gene and wherein the mouse exhibits any reduced

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level of spermatogenesis. The functional derivative of Bcl-w protein is not defined in the specification and a mouse with a reduced level of a functional derivative of Bcl-w is not described. The specification does not describe the claimed mouse having a disruption in a non-bcl-w gene, such as a bcl-w modulator (rox; see page 14, lines 9-18). The specification does not describe a reduced capacity to undergo spermatogenesis other than incapacity. The specification only describes a genetically modified mouse whose genome comprises a homozygous disruption of the bcl-w gene wherein no Bcl-w protein is made and the male mice fail to undergo spermatogenesis.

To help clarify the rejection, it is noted that it appears in some claims that Applicant may have intended to limit the scope of the genetically modified gene to that described in the specification (bcl-w). However, the claims fail to require that the genetic modification recited in the preamble be in the bcl-w gene. This correlation must be clearly established to overcome this rejection as well as those under enablement set forth below. For example, claim 18 is directed to a homozygous genetically modified male mouse comprising a mutation in the bcl-w gene. This claim does not require that the mutation in the bcl-w gene be the genetic modification that is homozygous and it does not require that the requirement for homozygosity be in the genetically modified gene. The written description rejection is directed to mice whose genome comprises a genetic modification other than that in the endogenous bcl-w gene. If this breadth is not intended, the claims should read "A mouse whose genome comprises a homozygous disruption of the bcl-w gene wherein no Bcl-w protein is produced in the mouse". The rejection is maintained as set forth in the paragraph bridging pages 3-4 of the office action mailed 11/15/2004.

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With respect to the breadth of the amount of Bcl-w protein produced, Applicant argues that the specification states that an animal having reduced Bcl-w "would have...reduced capacity to undergo spermatogenesis" and references the specification at page 8, lines 1-5. Applicant argues that the specification thereby supports the claimed mouse having any reduced level of spermatogenesis. Applicant argues that the law does not require an actual reduction to practice of every aspect of the claimed invention.

In response, the specification, at page 8, lines 1-5, is merely prophetic and is not an actual description of the claimed mouse. The art at the time of filing clearly held that the phenotype of genetically modified animals was unpredictable (see page 9, paragraph 2 of the office action mailed 03/09/2004). The mere statement of a phenotype other than that demonstrated and described for the mouse by the specification (incapacity to undergo spermatogenesis) is no more than that and fails to overcome the unpredictability of phenotype set forth in the art in a way to clearly establish that Applicant was in possession of the claimed invention at the time of filing.

*New Matter*

The amendment to claim 1 has necessitated the following rejection.

Claims 1 and 3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claim 1 contains the terminology "functional derivative". Literal support for this terminology is not found in the specification. Dependent claims 9 and 12 are not included in this

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rejection because they are limited to having a deletion of bcl-w or a mutation in SEQ ID NO:3, which is bcl-w, and is not a "functional derivative" thereof.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

#### *Enablement*

Claims 1,3,9,12,14,16-18 and 20 remain rejected, because the specification, while being enabling for a transgenic male mouse whose genome comprises a homozygous disruption in the nucleotide sequence encoding Bcl-w as set forth by SEQ ID NO:3, wherein the mouse exhibits an incapacity for spermatogenesis does not reasonably provide enablement for the other mice encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

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Applicant's arguments and amendments have been fully considered and are partially persuasive. Aspects of the rejection set forth on pages 4-8 of the previous office action are maintained for reasons of record as set forth below.

The aspect of the rejection with respect to the limitation to the claims regarding "47% similarity" (page 5, paragraph 2 of the office action mailed 11/14/2004) is withdrawn in light of Applicant's amendments to the claims.

The aspect of the rejection with respect to the claims encompassing heterozygous mice (page 5, paragraph 3 of the office action mailed 11/14/2004) is withdrawn in light of the new limitation to the claims requiring that the mice be homozygous for the genetic modification.

With respect to the aspects of the rejection pertaining to the breadth of phenotype of the claimed mouse (any level of reduced capacity for spermatogenesis) and the breadth encompassing any genetic modification of *bcl-w* resulting in any reduced level of Bcl-w protein Applicant argues that the specification describes a mutation that results in no active or substantially reduced levels of Bcl-w protein and references the specification at page 14, lines 9-18. Applicant asserts that one of skill in the art can readily make transgenic animals with mutant *bcl-w* resulting in a reduced capacity for spermatogenesis.

In response, the reference to the specification defines the term "mutation" and the definition encompasses many different types of mutations that cause loss of or reduced levels of Bcl-w protein. This reference is prophetic and does not support that the reduced level of Bcl-w protein leads to reduced capacity for spermatogenesis. As set forth above, the phenotype of genetically altered animals is unpredictable. Mere statement that a mutation will cause a phenotype is not sufficient to overcome this unpredictability. The specification has demonstrated



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that loss of Bcl-w protein results in total incapacity to undergo spermatogenesis. It does not support that a reduction in Bcl-w protein will result in a reduction of capacity to undergo spermatogenesis. The specification does not provide any teachings that indicate that the capacity of an animal to undergo spermatogenesis is directly proportional to the level of Bcl-w protein. The specification does not teach how to mutate the bcl-w gene, or any other gene, to merely reduce, but not eliminate, the level of Bcl-w protein or that a mere reduction in Bcl-w protein will lead to reduced capacity to undergo spermatogenesis rather than an incapacity to undergo spermatogenesis or no phenotype at all. The specification only teaches how to knockout bcl-w, or eliminate bcl-w gene expression. With respect to the phenotypic effect of loss of Bcl-w, the specification teaches only that the loss of Bcl-w protein results in an incapacity for spermatogenesis. The rejection is maintained for the above set forth reasons as well as those set forth at page 6, paragraph 2 of the office action mailed 11/14/2004.

With respect to the aspect of the rejection that the claims encompass a chimeric animal for which the phenotype is not known, Applicant argues that the phenotype of said chimera can readily be determined.

In response, while the phenotype of the animal (or mouse) can readily be determined a priori, the skilled artisan would not know what that phenotype will be, if any at all, and therefore, without evidence in the specification that the chimera will have a phenotype, the skilled artisan would not know how to use the claimed chimeric mouse. The claims now recite that the mouse is homozygous, indicating that the genetic modification has taken place in the genome of the mouse in all cells of the mouse. However, this language is awkward and does not clearly indicate what "homozygous" is referring to. The term could be referring to any locus of the mouse and

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therefore is not sufficient to overcome this aspect of the rejection. Suggested claim language that would address this and other aspects of the enablement rejection includes "A transgenic male mouse whose genome comprises a homozygous disruption of the endogenous nucleotide sequence encoding Bcl-w as set forth by SEQ ID NO:3, wherein the mouse exhibits an incapacity for spermatogenesis".

The following is a new grounds of rejection necessitated by amendment.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 14 is drawn to a method of making a homozygous genetically modified male mouse using method steps that, as claimed, result in a chimeric mouse. As set forth above, a homozygous genetic modification infers that the animal is a stable transgenic animal whose somatic and germ cells comprise a genetic modification. This inference is based on the fact that to obtain a homozygous genetic modification, two heterozygotes must be mated wherein the genetic modification is passed through the germline. Even if the mated heterozygotes were chimeric, any resulting homozygote would not be chimeric. The specification does not teach how to make a mouse homozygous for a genetic modification using the claimed method steps that will result in a chimera as claimed. The method steps of claim 14 result in a chimeric mouse wherein a proportion of the cells of the mouse comprise a heterozygous genetic modification. Therefore, the specification fails to enable making a homozygous mouse using the method steps

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as claimed because the resultant chimeric mouse, by definition cannot be a homozygous genetically modified mouse.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 20 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has argued that claim 20 no longer contains the objectionable terms. However, claim 20 continues to refer to a nucleotide sequence “substantially set forth in SEQ ID NO: 3”. The metes and bounds of this phrase are unclear and the rejection is maintained for reasons of record set forth on page 10, lines 3-8.

The rejection of claims 1,3,9,12 and 14 under 35 USC § 112-2<sup>nd</sup> paragraph are withdrawn in light of Applicant’s amendments to the claims.

The following rejection is necessitated by amendment.

Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: mating the chimeric animals (mice) to obtain the homozygous genetically modified male mouse. Without such a step, the methods do not clearly relate back to the preamble of the claim.

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***Conclusion***

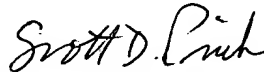
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio  
Examiner  
Art Unit 1632

  
**SCOTT D. PRIEBE, PH.D**  
**PRIMARY EXAMINER**